(3724) Husted & Bulman (DEN)	"With regard to the significance of the noxious influence of some particular occupations, the present material offers absolutely no suggestion of that kind. These patients, eight women and 27 men, came from all classes of society and represented a quite accidental mixture of all occupations, without predominant frequency of any occupation or group of workers. It is quite true that no mining is done in this country, but apart from one patient who was a stoker the material contains no cases of which it would be reasonable to assume that the patient had been exposed to the effect of dust and smoke more than all other persons in general. In this connection it is also to be mentioned that any marked degree of anthracosis of the lungs was found on two cases only. Tobacco has frequently been discussed as an etiological factor, but our patient material includes no tobacco workers, and according to the case records only four of the patients were particularly heavy smokers." (pages 152-153)
(3830) Bauer (PA)	"One patient (Case 21) the clinical record stated definitely that tobacco was not used. In fifteen the use of tobacco ranged from a few cigarettes to several packs or several cigars or the increased use of a pipe daily" (page 282). No other information was mentioned in records of 16 other cases of primary carcinoma of the lung.
(3833) Faget & Harmos (VA)	"All of our patients were heavy smokers." A total of six patients. (pages 22-23)
(3825) McGavack (NY)	"Fourteen of the 90 instances of pulmonary carcinoma here discussed were heavy smokers, using either a package or more of cigarettes, or four or more cigars daily. In all, 60 patients used tobacco to a greater or lesser extent. Summarization of the literature leaves one with the impression that the influence of tobacco in causing or predisposing to pulmonary cancer is highly problamatical." (page 132)

* Also referenced in Larsen's Tobacco Monograph (6101).
Note: The two-letter geographic abbreviation signify postal abbreviations of the United States; the three-letter are for foreign countries.

The above list is more comprehensive than the tobacco monograph by Larson, Silvette & Haag (6101). Only eight out of 31 entries are included in the tobacco bibliography. The eight publications selected by Harris are grouped

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further into nationality of authors from: Germany, Great Britain, Belgium, Austria and the United States.

German articles. The first suggestion that tobacco smoking caused lung cancer was attributed by Seyfarth (2421) to Brinkman & Engel. Lickint, from the Municipal Hospital of Kuchwald, Chemnitz, did not offer any original observations on patients but simply listed the following authors who "attribute at least partial blame to tobacco, particularly, cigarette smoking (2931):"

Berblinger: Klin Wschr 913, 1925.
Fahr: Verh pathol Ges Gottingen, 1923.
Ferenczy & Matolczy: Wien klin Wschr No. 19, 1827.
Hochstaetter: Klin Wschr 1092, 1926.
Kanngiesser: Bl f biol Med Hamburg, 1936.
Schönherr: Z Krebsforschg 27: 436, 1928.

I have not seen the above articles and an English translation will be needed to find out the number of patients and prevalence of smoking. Lickint indicated in his review that "for the increase incidence of lung cancer, a number of causes have been considered: better diagnosis, frequent occurrence of influenza, automobile combustion gas, street dust, road tar, combat gas and other." (page 10 of English translation of ref. 2931)

The 1930 publication of Mertens from the University Hospital at Munich, was a review of literature on increasing incidence of lung cancer. I cannot find the source of Harris' statement from the English translation (3031). The article was largely a description of experiments exposing mice to cigarette smoke, and are discussed under the next subtopic, together with German experiments on skin painting. It should be noted that prior to 1939, there were no specific figures on prevalence of smoking among German lung cancer patients and among the general population.

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British studies. The 1927 letter to the Editor by Tylecote (2719) has been discussed in Chapter II, pages 84 and 101. Brockbank's report that included smoking habit was intended to determine occupational incidence of primary lung cancer. In 62 cases investigated in some detail, nine (14.5 percent) seemed to have definitely dusty jobs, and eighteen (29 percent) worked among gases and fumes. Four were badly gassed during the war and nine smoked excessively. Brockbank concluded that "poison war gas, tobacco smoking, road dust and motor-car fumes are all possible aetiological factors." (page 37 of ref. 3222). He did not make any statement implying that there was a common denominator for all inhalants and that results of experimental studies were interchangeable.

Belgian studies. Thys, from the Foundation Medicale Reine Elisabeth in Brussels, wrote an article on the etiology of bronchial carcinoma (3540). In an effort to explain the increased incidence of lung cancer during the past two years (24 males, 1 female), Thys reviewed the literature starting with lung cancer in miners, and concluded with tobacco smoke. The reasoning Thys used appears to me to be similar to that used by his German colleagues during the 1930's and more recently, by Harris:

> "If we have just now insisted on the fact that iron, coal and slica mine workers are not particularly exposed to pulmonary cancer, we should nevertheless, remember that Sekoulitch, already in 1925, pointed out the frequency of cancer of the larynx in those who worked with wood. There again, is it a physical of chemical action with which we are dealing? Are the tannins and wood oils carcinogenic to the same extent as tar? Because tar, one of the most clearly carcinogenic agents that we know of, has of course also been used to explain the progressive increase in cases of pulmonary cancer. The theory which ties bronchial carcinoma to the action of dusts impregnated with tar which we can inhale daily on a more frequent basis is certainly interesting. We need only remember that from 1922 to 1929, the quantity of asphalt on the roads of France has increased from one to ten.

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Accordingly, we can see in the use of tar on these roads a carcinogenic cause of the first order which constantly grows in importance. But if bronchial cancer is caused by the inhalation of tar dust resulting from the asphalting of our roads, how can we explain its almost complete absence in women? It is therefore not there that we will find the explanation we are seeking.

But if it is effectively true that one must realistically incriminate the vapors of tar, at this point, we see, somewhere other than on the roads, a 'tarring' factor.

It is astonishing that publications dealing with pulmonary cancer have not yet mentioned tobacco smokers. In effect, when consuming tobacco, what are we ingesting if not a dry distillation of the cellulose which provides relatively strong quantities of tar.

We have long known about the irritative action which tobacco smoke has on the buccal mucous membrane. We spoke readily, a few years ago, of smokers cancer to designate the epithelium of the lips. But how do we explain that, having localized itself up to now in the buccal epithelium, this cancer now shows a marked tendency to displace itself toward the lower respiratory tract?

The explanation behind this sort of migration is simple when one thinks, as Professor Nolf has pointed out to us, about the difference in habits between yesterday's and today's smokers. In effect, just a few years ago, tobacco in our country was consumed mainly in a pipe; less in a cigar; cigarettes were rarely seen. At the same time, we reiterate, we were content to note a link between labial cancer (and lingual) and the irritation in the lips and tongue caused by the mouthpiece of the pipe and the tobacco smoke directly hitting the periphery of the mouth. The phrase 'Smoker's Cancer' was quickly coined.

Nowadays, in contrast, tobacco is mainly consumed in the form of cigarettes; the pipe has been abandoned and the average man today prefers a pinch of tobacco rolled in paper. The post-war period was the unprecedented fashion of the cigarette adopted by the masses. And it is precisely in this consumption of cigarettes, carried to excess, in which can perhaps be found the basic cause of pulmonary carcinoma. Because, in effect, with both the pipe and the cigar, the smoker is only 'tarring' his mouth (no inhalation); with the cigarette he is 'tarring' his bronchial tubes (total inhalation). This is because tobacco from a pipe or cigar gives off an acrid smoke which cannot be passed on into the lower respiratory tract without provoking a coughing fit. In contrast, cigarette smoke is not very irritating, often perfumed, and most smokers inhale it. This smoke undoubtedly penetrates very far, definitely entering into contact with the bronchial mucous membrane. This tar inhalation is even more dangerous for the bronchial epithelium as the very hot cigarette vapors are cooled far less than those of the cigar (which is longer and only two thirds consumed) or the pipe, in which the stem cools the smoke passing through and collects the tar which has been

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liquefied. In a word, this high temperture maintains the volatile state of the tars which would otherwise (in a cigar or pipe) be condensed and deposited prior to penetrating the organism.

If one therefore wants to admit the carcinogenic action of tobacco consumed frequently for a long time, it is ready for us to understand why, in one case, the neoplasia affects the lips or the tongue, in another, it is found in the bronchial tubes. With cigarettes and the deep inhalation of its smoke, one would almost be able to speak of tar applications on the bronchial mucous membranes, like the skin applications that we performed on mice in our cancer laboratories. We thus suspect the cause and frequency of cancer in men (95%), its rarity in women (5% from our statistics) who very rarely smoke or inhale the smoke. It was easy for us to state that in most cases, pulmonary cancers that we have examined, exist in heavy smokers and especially cigarette smokers.

Some will perhaps object by pointing out that there have been heavy cigarette smokers throughout history and that no one has noted in them the frequency of pulmonary cancer. But until these last few years, such smokers belonged to the leisure classes. So what is there to tell us that many of these smokers did not end their days because of undiagnosed cases of pulmonary cancer? For the attention of the doctor has only recently been drawn to bronchial carcinoma and it is probable that many of the cases involving private practice were not, and are still not, properly diagnosed as such (this diagnosis can only be made through the use of radiography or at the autopsy table).

In accordance with Professor Nolf, we again underline this point while recalling that the statistics of high frequency of pulmonary cancer are hospital statistics relating almost exclusively to cases among the working class. And, in this class, cigarettes have been in vogue only as of about the last twenty years; also, working class women do not smoke, or very little, which would explain why they are almost completely unaffected by this type of cancer.

In conclusion, it appears to us that a legitimate case can be made linking bronchial cancer, smoker's cancer of the post-war period, and the coming into fashion of the cigarette. This notion simply compliments the classic ones which attribute labial and lingual cancer to the pipe, an old form of smoker's cancer.

There would consequently be a new noxious action to be attributed to tobacco which would undoubtedly be useful to study more closely. In the fight against tobacco use, it seems to us that we are too often led to consider only the action of nicotine.

Notably Lickint (2931), in proposing regulations which have as their aim establishing restrictions on smokers, appears preoccupied only with the nicotine action of tobacco. And if it is true, as he believes, that it is time to call upon the press (through news conferences, etc.) to methodically educate the public on the dangers of tobacco use, it is perhaps also useful to mention to the public the potential role which the inhalation of tobacco

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smoke plays in the cause of lung cancer." (pages 2-4, English translation of ref. 3540)

Thys published another article in 1939 that needs translation (3939). It should be noted that there was a link of communication between Thys and Lickint in 1935 and it would be interesting to question if exchange of ideas continued after Belgium was occupied by the Nazis. I have not examined publications by Holf and Sekowlitch mentioned by Thys.

Austrian studies. Fleckseder, from Rudolfstiftung Hospital in Vienna, examined the records of 62 bronchial carcinoma patients admitted over the past 13 years (3627).

"Finally, I would like to focus on the influence of tobacco smoking on the development of BrCa (bronchial carcioma). 94.4% of the male patients admitted to smoking tobacco; 68.5% of them were heavy smokers. As already mentioned, the strong predominance of men over women in patients with bronchial cancer can most likely be explained by the abuse of tobacco so common in the large majority of our men (Lickint 2931). What could constitute the carcinogenic effect of tobacco smoking? Do we have to deal with an inhalation disorder which affects the bronchial membrane which has already been damaged by the breaking apart and transformation of cells or which, by means of precancerous transformation, causes the development of cancer in an initially normal mucous membrane. Or is it another case of vascular damage which prompts the growth of cancer by means of atheromatous changes on the small arteries of an already altered tissue area? In my opinion, a combined effect of both forms of disorder is most likely. The (part of sentence illegible to the translator) support a direct irritating effect of tobacco smoke on the mucous membrane. In this context, I would also like to note the tendency of smoker leukoplasia of the mucous membrane of the lips and the mouth to develop cancer. In the first case, mechanical irritants of the mouthpiece of a pipe, in the latter case an occasional luetic infection could play a role in the development of cancer (Scherber). The pronounced predominance of cancer of the throat in men can be interpreted in a similar manner as the predominance of BrCa in men. I would like to mention the observations of Brinkmann and of Enger, quoted in Seyfarth (2421), who observed the occurrence of bronchial cancer in cigar producers or cigar workers seven times. We have to assume that tobacco and its combustion products would have to affect the mucous membranes in a continuous manner and in a certain concentration in order to play a carcinogenic role. This explains

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the predominance of heavy cigarette smokers among our patients with bronchial cancer, since they inhale tobacco smoke in sufficient concentration into the main respiratory tract, while cigar and pipe smokers usually do not inhale tobacco as deeply. On the other hand, the fact that tobacco abuse promotes the development of arterio-sclerotic vascular changes is well known in hospitals and is fully confirmed by the observations which I have carried out to that regard for many years.

According to our observations of 62 cases of bronchial cancer, the following conditions are of principal importance for the development of a BrCa:

1. Damage in the area of the lungs and the primary bronchial tubes, which occurred prior to the development of the BrCa and which can cause the formation of scars, the separation and dispersion of cells, and possibly the alteration of the epithelium. Such previous damage was demonstrated in 100% of the cases. In our opinion, the most frequent cause in this regard is tuberculosis of the lungs and its lymphatic glands.
2. Vasoconstriction of the arteries which leads to oxygen deficiency in these damaged areas and which probably occurs in conjunction with arterial and age atheromatous hyperitonia and maybe also with lues and chronic lead exposure.
3. In women, a endocrine factor manifesting itself in a gonadal, functional disorder during climacteric and menopause. This condition is found in 100% of the relatively small number of our female patients with BrCa. This simultaneous influence of the vascular factor also needs to be considered here.
4. In the predominant majority of our male patients, abusive tobacco smoking, especially the smoking of cigarettes, which can be an epithelial irritant on the one hand and also cause vascular damage on the other hand." (pages 6-7, English translation of ref. 3627).

Statement 3 may have been extended as a proposed explanation for higher incidence of lung cancer in males than in females. There were animal studies that female sex hormones influenced carcinogenesis. However, this possibility was not seriously considered during the 1930's.

American clinical studies. There were three articles by American clinicians cited by Harris. My first question is as follows: What were the secondary references that might have influenced American clinicians to investigate the role of tobacco smoking? There were actually no reference to

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any German or European articles. It was possible that the Americans read foreign articles without alluding to sources.

Harris used the articles by Arkin and Wagner entitled "Primary Carcinoma of the Lung: A Diagnostic Study of 135 cases" (3613). This article was used not only as SOA ref. 6, Deposition Exhibit P6, but also Trial Proceedings Exhibit 51 (pages 822-823, 843-851; I do not have a copy of the cross-examination pages 5967-5969). The key sentence used by Harris was as follows: "ninety per cent of all our patients were chronic smokers and we believe that the inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or bronchioles." There was no mention of other etiologic factors.

Two years later, Arkin contributed a follow-up report on a larger group consisting of 160 cases of lung cancer. The article (not used by Harris), included a discussion, not only of tobacco smoke but also of etiologic factors:

> "Among the one hundred and sixty cases, one hundred and twenty, or seventy-five per cent have occurred between the ages of forty-one and sixty years. Fifteen patients or about nine per cent were twenty-one to forty years old. The disease is much more frequent in men than in women. There were one hundred and forty-five men, and fifteen women. Perhaps the inhalation of tobacco smoke is an important factor in causing chronic irritation with epithelial metaplasia in the bronchi or bronchioles. If this be true then the incidence in women should increase, now that women are smoking almost as much as men.
>
> We do not know the cause of malignancy in any tissue or organ at the present time. Chronic irritation, chemical, physical, or mechanical, may cause cellular damage followed by increased rate of growth. Hereditary predisposition plays a role in lower animals (Maude Slye), perhaps also in man. The human lung is exposed to numerous irritants, chemical bacterial and mechanical, any one or combination of which may cause the basal epithelial cells of the bronchi to undergo a metaplasia. These basal cells may produce three histologic types of cancer, (1) undifferentiated round or spindle cell, (2) adenocarcinoma, or (3) squamous cell." (page 370 of ref. 3846)

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In an earlier article, Arkin discussed the etiology of lung cancer as follows:

> "As in other forms of carcinoma, we do not know the exciting agent of bronchial cancer. Chronic irritation from smoke, dust, or chemical agents probably is the most important predisposing cause. To this must be added chronic suppurations as in bronchiectases or cavities, tuberculosis, syphilis, foreign bodies, and possibly influenza.
>
> Street dust, coal dust, stone dust, tobacco smoke, and especially exhaust fumes from gasoline and oil of automobiles have been blamed. We know the cancer-producing properties of certain coal-tar products, and perhaps it is these which cause chronic inflammatory changes with metaplasia of epithelium and cancer formation. The writer has seen 8 of 40 cases observed in the past seven years, in foundry workers who handled acid fumes, garage employees, stone-cutters, and people employed in dusty occupations. The increased use of gasolines, oils, and tar products may be an important factor in causing the increase in bronchial cancer in the last two decades. Fibroid processes in the lungs (tuberculous and non-tuberculous) with the formation of bronchiectatic cavities produce a chronic bronchitis, lead to the accumulation of purulent secretions and foreign particles. Epithelial thickenings, metaplasia, and leukoplakia form precancerous lesions. Perhaps here as in other organs a hereditary predisposition is a factor." (page 1256 of ref. 3032)

It should be noted that contrary to Harris' impression, Arkin did not subscribe solely to tobacco smoking as a cause.

Several colleagues of Arkin in Chicago did not mention tobacco smoking in their publications on lung carcinoma: Stein & Joslin (3815) from Veterans Hospital at Hines, Illinois and others listed in the Table of Case Reports (3817, 3818). The following clinicians used Arkin & Waagner as a secondary citation: Volini & Shapiro of Cook County Hospital (3816), McGavack from New York City (3825), and Faget & Harmos (3833) from the U.S., Marine Hospital at Norfolk, Virginia. However, Faget & Harmos referred to the tobacco literature "in causing or predisposing to pulmonary cancer is highly problematical."

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Editorials on lung cancer. The Lancet published two editorials on the subject of cancer of the lung. Boycott commented on increased incidence as follows:

> "In the second place, we have had an interesting problem in aetiology to solve and we still have it. Numerical analysis of the more complete data (such as J.B. Duguid (2721), did for the records of the Manchester Royal Infirmary) seems to show that the recent increase began long before pathologists took notice of it - somewhere about 1890 or 1900. If that is so, the influenza of 1918-19 and war gases can have had nothing to do with it. Presumably, therefore, the increase has been caused by some change in habits or mode of life or environment. In speculating what this might be, we cannot put aside the very definite evidence, clinical as well as experimental, that an irritant must act for at least about a quarter of the natural span of life before it produces a tumour; the latent period for mule-spinners' cancer is at the least 15 and on the average 35 years of exposure to the effective mineral lubricating oils. These data, it is true, apply to epitheliomas of skin and may not be directly transferable to tumours of mucous membranes. But something of the same kind must surely be true for these also, and in looking for the cause of bronchial cancer we should probably consider what happened towards the end of last century. The environment as a whole has become less carcinogenic; there is more soap and hot water, less irritating food, the air is cleaner, the general standard of life has greatly improved. We have, on the other hand, much more tobacco and more recently petrol engines and tarred roads; whatever the agent, it produces lung cancer much more frequently in men than in women." (page 959 of ref. 3225)

The above editiorial combined as "irritants", tobacco, petrol, engine emissions and tarred roads in the environment. The second Editorial also appearing in Lancet continued:

> "From centres in nearly all the populous districts in the northern hemisphere we now have reports of a progressive increase in the incidence of cancer of the lung. To the April issue of the Wiener Archiv für innere Medizin Dr. Dinko Sucic contributes a paper on its occurrence in Zagreb in Yugoslavia. His material comprised in all 51 cases, 30 of which were investigated in the pathological institute of Zagreb University during the last ten years. In that institute lung cancers have increased from an average of less than 6 per cent. of all cancers in 1923-25 to more than 18 per cent. in 1929. Such an increase is no unusual finding, but this record is important in view of the fact that

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Yugoslavia is an agricultural State with (as Sucic points out) 80 per cent. of its population engaged in farming and the like. This goes to show that the increase in pulmonary tumours is not confined to the populations of the air-polluted industrial centres of the world.

The fact of its increasing incidence makes cancer of the lung particularly interesting to pathologist at the present time, for one may reasonably assume that as the disease is on the increase so must the factors which are responsible for it be on the increase, and hence be the more readily identifiable. On this assumption a number of extraneous agents, associated with the modern increase of industrialism, have been cited as possible causes. These include road dusts, especially from tarred roads, exhaust gases from motor-cars, and factory smoke - all acting through the medium of air pollution. Yet the now well-established fact that these cancers are on the increase in agricultural lands as well as in industrial towns makes it difficult to associate them directly with industrialism, especially as these industries in the various countries concerned are so diverse. Sucic is driven to the conclusion that diverse factors must be concerned indirectly in the carcinogenesis, all of them acting as irritants to the bronchial mucous membrane or alveolar epithelium so as to predispose to cancer development. It is difficult to believe, however, that even a variety of factors could operate with such uniform effect in such diverse places, both urban and rural, as has been the case with the increase in cancer of the lung. One can believe that the atmosphere of large cities may have deteriorated in the last few decades, but not that the atmosphere in the countrysides can have altered correspondingly, and the simple fact that the cancer increase is so general and uniform seems largely to absolve industrial air pollution from blame. A factor which is of much more uniform distribution than industrialism and which merits careful consideration is tobacco-smoking. Already several authorities have suggested this - and especially cigarette-smoking - as a likely cause of lung cancer, and the notion is certainly gaining ground; yet there remains an evident reluctance on the part of many investigators to associate themselves with it. Hoffman (3131) has discussed the question fairly fully, and amongst other notable facts he has pointed out that the consumption of light cigarettes has increased from 53,000 million to 108,000 million between the years 1918 and 1928. There is no doubt that men still remain greater tobacco-consumers than women, and the fact that practically all observers find cancer of the lung to be preeminently a disease of men, suports the suggestion of a direct relationship between it and smoking. Sucic noted that 25 of his 30 cases were in men, and many other observers have found the proportion in favour of men to be even greater than this. If air pollution of any kind is to be seriously considered, therefore, this particular form of it must not escape attention for, no matter whether he be in the fields of Yugoslavia, on the

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> mountains of Innsbruck, or in the streets of Manchester, the cigarette-smoker who inhales habitually subjects himself to the most concentrated form of air pollution possible to endure.
>
> Unfortunately, information about the personal habits of past cases is difficult to obtain, so that the data which might yield direct evidence on this point are wanting, and the answer must await the collection of further clinical observations. Several workers have of late tried to produce experimental proof that tobacco is carcinogenic - using such methods as subjecting animals to an atmosphere laden with cigarette smoke, or applying to their skins tar obtained from tobacco combustion. A feature of many of these experiments seems to have been the development of cancer in not more than one animal out of large numbers used in each instance. Such was the case with two independent workers in Germany and the Argentine and also with a group of workers in Birmingham whose results have lately appeared. These negative results are, of course, from the nature of things biological, just such as are to be expected in early attempts at a new line of experimental cancer production, and it would be wrong to conclude from them that tobacco is unimportant as a factor in the causation of cancer. However difficult it may be to prove the case against cigarette-smoking, it has not yet been cleared from suspicion." (pages 1206-1207 of ref. 3226)

Until 1932, results of animal experiments did not support "tobacco tar" as a cause of cancer but were positive for coal tar. The discussion on tobacco use in agricultural areas was not documented by consumption figures. The third Editorial appeared in JAMA a year after the appearance of an article by Arkin and Wagner (3613):

> "Among the contributing factors to this increase, the injurious effects of tobacco smoking, exhaust gases from automobiles, tar on roads and the influenza epidemic of 1918-1919 have been suggested. None of these can be accepted as definitely causative. Arkin and Wagner (3613) state that 90 per cent of their patients were chronic smokers. They believe that inhalation of tobacco smoke may be an important factor in producing chronic irritation with epithelial metaplasia in the bronchi or broncioles. The disease is preponderantly more common in males than in females, about two thirds of all cases occurring between the ages of 40 and 60. Occupation probably does not play an important part and evidence regarding the influence of preexisting pulmonary disease is not convincing. Edwards emphasizes the fact that in a number of his patients the history was peculiarly free from illness in any form. A persistent cough, hemoptysis and thoracic pain of a severe and continous type, in a man past the age of 40, are highly suggestive of pulmonary cancer. However, many of the cases of pulmonary carcinoma may be without pulmonary symptoms, their

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earliest manifestations being those of the metastases away from the thoracic cage. Thus, in Arkin and Wagner's series of 135 cases, 51 percent presented extrapulmonary signs and symptoms and only 49 per cent presented symptoms referable to the pulmonary tissue.

Recent histologic studies of malignant lesions of the lung have demonstrated that most of the round cell, 'oat' cell and spindle cell sarcomas of the lung are in reality carcinomas of bronchogenic origin. The majority of the carcinomas of the lung are of the squamous cell type. Tuttle and Womack (2424) call attention to the facility of the bronchial epithelium to change its morphologic characteristics when subjected to trauma or chronic irritation. The hyperplastic and metaplastic changes taking place may in reality be the first step in carcinogenesis. Attractive as this theory seems, it has found little support in clinical facts. Tuttle and Womack themselves state that of the seventy-six cases of primary bronchiectasis in persons of the cancer age seen in the chest service of the Barnes Hospital there has been observed only one patient who subsequently developed bronchogenic carcinoma. Bronchopulmonary carcinoma displays a tendency to give rise to metastases to the liver, bones, spleen, pancreas and, with a characteristic freequency, to the suprarenals and the brain. According to Tuttle and Womack, tumors of the major bronchi give symptoms early, extend more slowly and are more amenable to surgical treatment, while tumors of the minor bronchi and of the periphery of the lung cause fewer early symptoms and are more rapidly fatal." (page 1716 of ref. 3730)

Smoking habits of population groups. Hoffman interviewed non-cancer patients in San Francisco, suffering mostly from chronic diseases of adult life, chiefly, heart disease, arteriosclerosis, arthritis, hypertension, diabetes, nephritis and other diseases. From responses of 537 male patients, 42.3 percent reported themselves as "heavy smokers" which is comparable to 45.6 percent for cancer patients. Hoffman concluded that "the differences are therefore very slight, which may be construed as opposed to the theory that smoking habits increase materially the liability to malignant tumors." Hoffman commented further:

"In cancer of the lungs the effects of tobacco smoking are more difficult to prove but there is not the slightest question of doubt as to the fact that those who practise inhaling certainly drive the smoke into the innermost recesses of the lungs. The

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> observed increase in cancer of the lungs during recent years is highly suggestive of its correlation to the immense spread of cigarette-smoking habits. In the English statistics the mortality from cancer of the lungs for 1927 was at the rate of 26.8 for men and 9.7 for women. Here again the disparity in sex susceptibility is highly suggestive of smoking habits as a causative factor. But cancer of the lungs has been attributed to a variety of modern conditions which may account more or less for the observed increase which cannot be entirely, at least, attributed to better diagnosis. In England and Wales cancer of the lungs has increased in males from 0.2 during the ten years ending with 1910 to 26.8 during the year 1927. In females the rate has increased during the same period from 7.0 to 9.7. Yet smoking habits have proportionately increased faster among women during recent years than among men. But the fact must not be lost sight of that the injurious effects of tobacco smoking in their relation to cancer probably require quite a long period of time to become noticeable. Since I have dealt with the question of cancer of the lungs in a separate discussion published in the American Jornal of Tuberculosis (2911), I will not enlarge upon it on this occasion, except to say that personally I am strongly of the opinion that a relation between the increase in smoking habits and cancer of the lungs may safely be assumed to exist. I have never been inclined to accept the view that the increase in lung cancers during recent years is chiefly attributable to the after-effects of the influenza epidemic. As observed in the Journal of the American Medical Association of February 13, 1916, the clinical records in a large proportion of the investigated cases did not show any history of influenza." (pages 61-62 of ref. 3131)

Hoffman wrote a monograph on Diet and Cancer, which suggested that he was personally committed to dietary factors in causation of cancer (see Topic E). The prevalence rate of tobacco smoking of non-cancer patients reported by Hoffman, i.e., 42 percent heavy smokers, are comparable to results of Fortune Magazine survey conducted in the 1930's. The question asked was "Do you smoke cigarettes?" without qualifying to heavy or moderate or light. In the Fortune survey, 52.5 percent of all males interviewed answered "yes" which would include heavy smokers and otherwise (3541).

It was apparent that prior to reporting results of a 1939 case control study, the available studies indicated that the prevalence of tobacco smoking

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in cancer patients was no higher than that of non-cancer patients and general population. Initial control studies are described in Chapter IV.

Experimental carcinogenesis.

In Harris' SOA report, there were 18 summary statements under the group title of "Experimental and Chemical Studies 1900 to 1947." My general plan is to discuss the opening three statements (4.1 and 4.2), and then proceed to those relating to tobacco tar (4.5 to 4.9). The statements on urinary bladder carcinogen (4.3) and on coal tar (4.4) are discussed in greater detail under Topic D heading of "Occupational and Environmental Factors." Statements summarizing progress during the 1940's (4.10 to 4.18) are covered in Chapter IV. The opening summary statements in Harris' SOA report were as follows:

> "4.1. Scientific articles concerning the potentially cancer-caausing effects of tobacco products on laboratory animals date back to 1900. (See references in Schurch and Winterstein 1935, 1937; Muller 1939; Campbell 1939; Sugiura 1940; Flory 1941; Ebenius 1943; Wynder, Graham and Croninger 1953; Graham, Croninger and Wynder 1957; Wynder 1955; Wynder and Hoffman 1967)
> 4.2. Such experimental attempts to induce cancer in laboratory species with tobacco products were motivated, in great part, by the clinical literature linking tobacco and cancer (e.g., Roffo 1930b, 1937b; Cooper et al. 1932).

Although the Tobacco Monograph (6101), was a reference cited elsewhere in Harris' SOA Report, its authors (Larson, Haag & Silvette) were not included as a reference under the subject of experimental carcinogenesis. I do not agree with Harris because the Tobacco Monograph contained a thorough discussion of publications relating to the above summary statements. Since more than half of articles on experimental carcinogenesis are in Spanish or German, it is

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difficult for me to improve or paraphrase the description by Larson, Haag & Silvette, who examined all published articles.

Roffo's rabbit experiments using tobacco. During the 1930's, the most prolific writer on "tobacco tar" as an animal carcinogen was Professor A. N. Roffo, Director of the Institute of Experimental Medicine for Study and Treatment of Cancer of the University of Buenos Aires. There were more than 250 articles published from 1920 to 1935 by Roffo and his associates (see Index to the Literature of Experimental Cancer Research 1900-1935 submitted as Enclosure G). Larsen, Haag & Silvette listed 45 publications of Roffo relating to tobacco and cancer published from 1930 to 1950, and 17 were cited by Harris. Larsen, Haag & Silvette overlooked a dozen articles by Roffo and his collaborators on the subject of experimental skin tar cancer.

Harris, in his SOA Report, summarized the contributions of Roffo as one who applied chemical and biological techniques for studies on "tobacco tar."

> "4.5. In the 1920s and early 1930s, experimental scientists had found that carcinogenic tars could be formed from the pyrogenous products of a variety of organic materials (Kennaway 1925; Kennaway and Sampson 1928; Watson 1933). Given the clinical evidence on tobacco and cancer, it was logical that a carcinogenic tar could likewise be formed during tobacco smoking (e.g., Cooper et al. 1932; Bogen and Loomis 1932; McNally 1932).
>
> 4.6. Following such logic, Roffo published an extensive series of papers on tobacco carcinogenesis in Spanish, German and French language scientific journals during the 1930s (Roffo 1930ab, 1931ab, 1932, 1936, 1937abcd, 1938, 1939abcd, 1943). Roffo's findings were cited repeatedly in the world scientific literature, including English language journals (McNally 1932; Campbell 1939; Ochsner and DeBakey 1941; Flory 1941; Editorial 1941; Menne and Anderson 1941; Grace 1943, 1944; Ochsner 1945).
>
> 4.7. Among Roffo's experimental findings were: production of oral leukoplakia after exposing rabbits to tobacco smoke (1930a); production of an infiltrative, metaplastic epithelial tumor after 8 months of painting rabbit ears with the water-soluble components of tobacco smoke (1930b, 1931a, 1937d); failure to produce such a

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> cancerous lesion by aplication of nicotine alone (1930b, 1931a, 1937d); production of a metastatic carcinoma in a rabbit exposed for 3 years to a jet of whole tobacco smoke (1931b, 1932); production of squamous cell carcinomas in multiple experiments by 8 to 14 months' of application high-temperature, destructive distillates of various types of tobacco (1936, 1937abcd, 1938, 1939ac); induction of neoplasms in rats with implanted pellets of tobacco tar (1936); spectroscopic identification of benzo(a)-pyrene in the tobacco distillates (1937b, 1939bd); production of squamous cell cancers in rabbits after 12 months' application of tars prepared from condensed tobacco smoke (1939e); and production of lung cancer in rabbits after direct injection of tobacco distillate into the lung (1943)."

The most important criticisms to Roffo's group of articles are: (a) The publications were repetitive in contents; (b) Rabbits were used, instead of mice and rats used by European and North American researchers on coal tar skin cancer, and by Roffo himself on ultraviolet skin cancer; (c) The publications citing Roffo's work did not exceed twenty, including the nine mentioned in Harris' Summary Statement 4.6. During the 1940's, additional publications by Roffo and his Latin-American contemporaries appeared and are reviewed in Chapter IV.

Beard et al wrote a 1936 review entitled "Experimental Production of Malignant Tumors in the Albino Rat by Means of Ultraviolet Rays." It is necessary to recall the research conducted by Roffo that started in 1916, so:

> "Roffo has been interested in the cholesterol content of neoplasms for many years. In 1916 he showed that a rat tumor may contain over twice as much cholesterol as is found in the whole organism of the host. The normal skin of the face may contain three to six times as much cholesterol as that of the abdomen. It was further observed that the large amount of cholesterol in the face resulted from the exposure to sunlight. Roffo and Pilar then exposed rats to sunlight and ultraviolet light. Increases of 23 to 100 per cent in the cholesterol content of the skin occurred. It was suggested that cholesterol prepares the soil for subsequent malignant growth by acting as an accumulator of light.
>
> Further work by Roffo is interesting in this connection. He exposed rats to ultraviolet irradiation, beginning with a five-minute daily dose, which was gradually increased to twenty hours daily. The latter dose was given from six to eight months. Tumors on the eyes, ears, and back of the head were produced. Later

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600 rats were exposed to direct sunlight for five hours. Of these, 365 died of sunstroke in a day; 165 of the remaining 235 developed tumors within ten months. The animals were fed a stock diet of bread and milk. The areas affected were those unprotected by hair, and the histologic form differed with the seat of the tumor. Spindle-cell sarcoma developed on the conjunctiva of the eyes and carcinoma on the nose and forefeet. Of the tumors on the ears, 58 per cent were carcinoma, 36 per cent spindle-cell carcinoma, and 6 per cent carcinosarcoma, while on the eyelids 50 were carcinoma and 50 per cent spindle-cell carcinoma. From the results of experiments with rays from different sources, the cancer-producing action is believed to depend more on the actinic intensity of the ultraviolet wavelength than on the quantity of rays. Local hypercholesterolemia was noted one day after exposure and before any skin lesions appeared.

Findlay exposed 20 mice to ultraviolet rays after removing the hair from certain areas with sodium sulfide. Typical epitheliomas were produced. Similar results have been obtained by Herlitz, Jundell and Wahlgren, using white mice. Putschar and Holtz also obtained epitheliomas of the ears under similar conditions without depilation. They believe that there are close histologic relations between ultraviolet ray cancer and the precancerous light dermatoses that may occur in man, and are convinced that their experiments show the etiologic role of ultraviolet rays in skin cancer in human beings.

Roffo next exposed rats and mice to the entire range of solar rays for a period of nine to ten months and produced typical carcinomas and a fusocellular type of sarcoma. An epithelioma of the ear began as a hyperkeratosis which at the end of about eight months' exposure had developed into a typical carcinoma. The sarcomas usually developed without prceding into a typical carcinoma. The sarcomas usually developed without preceding keratosis. There were 140 tumors on the ears, 58 on the eyes, and 15 on the paws. Histologically the eye tumors had the appearance of a spindle-cell sarcoma. Roffo stated that a biochemical change in the form of a hyper-cholesterolemia takes place as a result of the exposure to the ultraviolet rays of the sun. This results in the transformation of the normal into a neoplastic cell.

Much publicity was given to Roffo's report, and the Academy of Medicine of Paris appointed a committee consisting of Roussy, Hartmann and Beclere to verify the above findings. Roffo's work was confirmed, and the potential danger of excessive exposure of the individual to sun baths was stressed by this committee." (pages 258-259 of ref. 3637)

It should be noted that Roffo's controversial work on rat skin cancer was later indicated. His work on rabbit skin cancer continued to be a controversy

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because subsequent investigators used mice and rats, just as Roffo did in his experiments using ultraviolet. It is not clear to me why Roffo used rabbits in his "tobacco tar" experiments.

Harris defended the above Summary Statements in his Oral Deposition, Transcript of Trial Proceedings, and Experts Responses to Requested Information (ERR pages 26-28). Roffo's accomplishments were defended by Harris, and enumerated the authorities who subsequently agreed with the original findings that tobacco tar painted to skin of experimental animals caused new growths. There were criticisms of Roffo's technique that appeared in the 1940's and the 1950's but they were ineffective because of additional positive findings in mice and rats that were essentially similar to results of Roffo's rabbit experiments. I recommend that a trilingual expert, preferably an epidemiologist (like Najera) be requested to review all publications of Roffo, all conflicting articles on experimental pulmonary carcinogenesis, and the relevance of experimental skin carcinogenesis to human lung cancer. Until a trilingual expert can complete an evaluation of Roffo's experiments, I suggest that the following summaries prepared by Larsen, Haag & Silvette be used:

> "An extensive study of 'tobacco' carcinogenesis in the rabbit was begun by Roffo about 1930, and continued for a dozen years and more. In some of his earliest experiments, he gave rabbits daily injections of tobacco-smoke into the gum, and after 25 days, observed lesions with the characteristics of a plaque of leukoplakia at the site of application (3034, 3035). He ascribed this result to the action of the resinous substances produced by pyrogenous distillation. Previous daily injections of a colloidal solution of cholesterol were said to shorten the period of tobacco treatment before the appearance of leukoplakia. This author then investigated the carcinogenic effect on the rabbit ear of tobacco-smoke (3228, 3229), tobacco-smoke solution (3036, 3127), and various preparations of tobacco tar produced by destructive distillation (3646, 3731, 3733. 3847. 39346, 4316), and also from tars similarly prepared from coffee (3940, 3941), tea (4012), and yerba mate (4111). The incidence of cancerous lesions in these

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experiments is shown in Table 13-1. The characteristics of the tumors produced were described in detail, and photomicrographs reproduced (3034, 3228, 3646, 3733, 3940, 3941, 3946); and in summary, Roffo (3945) stated that the evolution of the lesions was more or less the same with all the tars, including non-tobacco tars: the lesions began with hyperkeratosis and papillomas which, within 9 or 10 months, changed to infiltrative Malpighian epitheliomas, with invasion and destruction of the organ; the histological type was that of a prickle-cell carcinoma presenting sometimes a marked anaplasia. Although tars produced from coffee, tea, and mate were found to be as carcinogenic as tobacco tars, Roffo pointed out that the former substances presented no danger, since they were prepared as infusions in which tars are insoluble. Coal-tar produced the same carcinomatous tumors on rabbit ears as tobacco-tar, but the latter was said to be more active (in contra-distinction to comparative results obtained by many investigators on mouse skin), and animals which tended to be resistant to tobacco tar were also resistant to coal-tar (4013). All but one of the tumors produced by application of tobacco-tar to the ear of rabbits (the figure of 1000 animals is given, but this apparently refers to the total number of animals used, rather than to the number of tumors found) were said to have had an epithelial histo-pathogenesis, the exception being the production in 1 animal of a tumor corresponding to the histopathlogical type of fusocellular sarcoma, demonstrating the capacity of tobacco-tar to exert a carcinogenic action on the connective tissue as well (4212). A malignant and metastasizing carcinoma was described in great detail (4312, 4315, 4412), and still another malignant tumor was the subject of a special description (4314). Before leaving the subject of Roffo's animal experiments, it should be mentioned that this author did not appear to use pure strains of animals, and that the incidence, if any, of spontaneous ear tumors in control animals was unknown or unreported. Thus, the 'production', by tobacco-tar application in only 1 animal out of 1000 of a 'sarcoma' or of 1 or 2 apparently extraordinary malignancies, may, for all one can tell, be within the incidence-rate of spontaneous tumors; it seems clear, however, that such tumors were not produced in any scientific or experimental sense of the word; and one must therefore be very hesitant in placing too great weight on Roffo's reiterated description of a solitary tumor.

Roffo (3646, 3733) tested the carcinogenic properties of 3 fractions derived from the destructive distillation of tobacco, the first between 100-120°C., the second between 120-135°C., and the third consisting of the residue from this distillation. The second product was considered to be the most active on chronic application to the rabbit ear, 15 or 16 rabbits surviving for more than 7 months having developed tumors from product 2, and 70% of 20 animals from product 3 (3733). Oil distilling above 380°C. from tar obtained by destructive distillation of dry tobacco leaves also uniformly produced malignant tumors when painted on

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the ears of rabbits (3948). All tobaccos in commerce yielded the same type of carcinogenic tar (4015). As judged by the carcinogenic effects of chronic application of the 120-350°C. fraction to rabbit ears, carcinogenic potency was greatest for tars derived from Turkish, Egyptian, Kentucky, and chewing-tobacco, and less for tars derived from Havana, Italian, Corrientes, Paraguayan, German, and Salta tobaccos, although even the latter produced at least 50% tumor formation (3944, 3945, 3947). Light tobacco produced a larger quantity of tar than black tobacco, and the tar was also more toxic; but both produced about equal percentages of cancers in treated rabbits (3848). Red tobacco produced a larger quantity of tar than black tobacco, and the tar was also more toxic, although both produced tumors in 80-90% of the animals tested (4011). Exhaustive extraction of tobacco with organic solvents (alcohol, chloroform, acetone, petroleum ether, paraffin, and benzene) prior to the preparation of tobacco-tar resulted in products which showed little carcinogenic activity (4213). Tobacco-smoke filtered through water (with a narghile) or through cotton still yielded a carcinogenic tar, although the latter was less in amount that with unfiltered smoke (3943). Roffo (4213) felt that the precursors of the carcinogenic tobacco-tars were chiefly phytosterols, and these could be extracted from tobacco by organic solvents, and the tar produced by combustion of such extracted tobaccos was relatively non-carcinogenic. This concept was said to be supported by the quantity of phytosterols in tobacco leaves (about 0.53% of the dry matter in black tobacco, and 0.78% in light tobacco), a quantity which is rather high in comparison with the extracts obtained from other plants entering into the human diets (e.g. 0.15% in potatoes, 0.12% in cabbage, 0.20% in oats, and 0.16% in pumpkins). Roffo (3942, 4211) described the isolation of a product from tobacco tar which displayed the spectrographic and fluorescent properties of 1,2-benzpyrene, and presented all the physiochemical properties of the synthetic substance; experiments on rabbits demonstrated that this product was strongly carcinogenic." (pages 422-424 of ref. 6101)

In most of his publications, Roffo recalled the high prevalence of tobacco smoking in cancer patients in general, and in those with oral, laryngeal or lung cancer in particular. Although all of his articles were in Spanish, French or German, most of them contained a summary in English. There is a brief article entitled "Universal Toxicomania of Tobacco" (4115) that was presented as an exhibit during Harris' deposition (pages 420-429, DTH). The 3

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pages of text and illustrations have appeared in several of Roffo's scientific publications. Where did this 1941 article come from? What Journal? All of Roffo's articles dated 1940 and later are submitted as part of Chapter IV. Prior to availability of Chapter IV, it is pertinent to quote comments in a 1941 article:

> "The tobacco tar and the coal tar, if applied on the ears of rabbits, produce both the same carcinomatous tumours.
>
> On studying the tumoral lesions developed in these animals, one states that the neoplastic growth is more active, and consequently more malignant, in the ears of tobacco treated animals than in the coal tarred ones.
>
> This observation can be made at simple eye-sight, the tobacco tumours being much more voluminous, cellular and numerous, while those provoked by coal taring are more papillomatous and of marked cornification.
>
> In the present experimentation, we wish to point out a very interesting fact in relation to the biological ground; it is the steady relation of tumour production in both ears.
>
> The rabbits 1, 2, 4 and 5 and especially 7, show, for instance, a strong quantitative resemblance of their tumours production in both ears. The last mentioned one presents a very abundant tumour production, on one ear as well as on the other, while in the animals 8, 9 and 10 this production is a most limited one; in fact, we did not observe on each ear of these animals more than 1 or 2 minute papillomata.
>
> This phenomenon once more proves the importance of the biological ground in the cancerization of tissues, in the presence of a carcinogenic agent; the animal which has a biotissular predisposition, has it for one ear as well as for the other.
>
> On the other hand, there is another remarkable result which is in relation with the focus of cancerization under the direct action of a carcinogenic agent because the cancerization of one ear by one of these does not necessary exclude the cancerization of the other by one of those, providing that the host has a constitutional inclination towards cancerization.
>
> The experimental fact is related to another one which I already published in 1916, in a communication on my experiences with transplantable tumours in white rats.
>
> I described there that on inoculation of the same host with two grafts of the same tumour both develop in the same manner; and even if the grafts were taken from histologically different tumours, their development is alike, although each conserves the histological structure of the respective primary tumour.
>
> Moreover, the present experimentation establishes the carcinogenic unit of all the tars in general, of whatever origin they may be.

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> I already studied this matter in an earlier paper in connection with the carcinogenic unit of all the ears extracted from different tobacco types, a study which has been completed lately by experiments with coffee and tea tars.
>
> All these tars present the same physico-chemical characters as the coal tar, especially as to the spectrography and fluorescence." (pages 1011-1012 of ref. 4116)

The above article, with an English summary, was one of several missed by Larsen, Haag & Silvette, and also by Harris. During the 1940's, the techniques used by Roffo for identification of benzo(a)pyrene was criticized. However, the identification of benzo(a)pyrene in tobacco tar by other investigated has muted the question whether Roffo used an acceptable procedure.

Additional rabbit experiments. Prior to and during the 1930's, seven laboratories tested tobacco tar on rabbit ear with essentially negative results. The description by Larsen, Haag & Silvette was as follows:

> "In the [apparently] earliest reported experiments on rabbits, Wacker and Schmincke (1101) obtained tobacco-tar by washing heavily tarred smoking-pipes with alcohol, then evaporating the alcohol and dissolving the residue in fat or oil, or else steam-distilling the residue and treating it with ether before preparing an oily solution. They injected this substance into the ears of rabbits, and noted that extensive growths resulted, histologically resembling very strikingly squamous-cell carcinoma. Helwig (2720, 2827) duplicated the work of the preceding investigators, but reported that, although an atypical proliferation took place, there was never an actual malignant transformation.
>
> Schurch and Winterstein (3542) (see also Schurch 1935, 1936) treated 12 rabbits on both ears twice weekly with nicotine-free cigar-smoke tar for 220 days, but no disturbances of hair or skin resulted. Following this experiment, the same animals had the mouth treated with the tar, 3 times a week for 1.5 years, and again no abnormalities were noted. In rabbits generally damaged by being placed on a high cholesterol diet and by being previously treated with coal-tar on one ear to the point of obvious changes, tobacco-tar painting of the opposite ear produced in some instances tumors and cancer within 1-5 years. The accelerating effect of coal-tar or cholesterol had previously been described by Lu-Fu-hua (3447). Schurch and Winterstein (3734) pointed out the importance of the time factor with tobacco-tar; the cancer-provoking action of tobacco tar was said to be small, but when acting over a long period of time, it may cause more cancers and precancerous lesions

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> than most contemporary work would have it believed. The contemporary work referred to by Schurch and Winterstein was apparently that of Bogen and Loomis (3227), Lü-Fu-hua (3447), and Sugiura 1940, all of whom failed to produce any cancerous change in the ears of rabbits painted with tobacco-tar for periods up to 6 months. On the other hand, ear papillomas or cancers were produced by similar treatment with gas-house tar (Bogen and Loomis, 3227) or by coal-tar (Lü-Fu-hua, 3447). Chickamatsu and Katsunuma (3129) appear to have demonstrated a canceroid on the ear of a rabbit produced by continued application of tobacco-tar for 225 days; histologically, this was said to be a typical carcinomatous infiltrating growth; neither metastases nor 'taking' of transplants was observed. [This article appears to be an abstract of a demonstration, and no mention is made of the number of animals treated to produce the one demonstrated lesion]" (pages 422-423 of ref. 6101)

The discussion of rabbit experiments continued through the 1940's. It became apparent a decade later that rabbit ear painting was less favorable for experimental carcinogenesis compared to other animal species.

Experimental carcinogenesis in mice. The first publication on exposure of mice to cigarette smoke was reported by Mertens, from the University Hospital of Munich (3031). The exposure schedule reflected a trial and error approach. Of the 125 mice that entered the experiment, 28 were still alive 22 months later. Some died from convulsive effects of smoke. One mouse developed bronchial carcinoma but Martens doubted whether it was caused by exposure to smoke.

With the exception of Merten's experiments, those conducted by other investigators consisted of applying or painting "tobacco tar" to skin of mice. The technique originally was applied to coal tar for the purpose of identifying carcinogenic substance involved in tar skin cancer in humans. The investigators using "tobacco tar" intended the results in mice to apply to oral cancer but later researchers applied results to lung cancer in humans. The review of

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skin painting experiments by Larsen, Haag & Silvette contained the following description:

"A. Leitch (2221, 2322) conducted experiments in which application of nicotine-free tarry material prepared from artificial pipe-smoke to the skin of mice for many months led to epilation and chronic ulceration of the areas of application, but without any neoplastic reaction in a single case. Therefore, he did not consider tobacco-smoke tars a specific irritant of the tumor-producing class.

Helwig (2720, 2827) painted nicotine-free ethereal extract of tobacco-tar from briar pipes on the back of the heads of 50 mice, 3 times a week over a period of almost 1 year. Although ulceration of a rather marked degree was produced, no atypical growth was ever encountered in sections taken at intervals from these ulcers. In further experiments, ether and chloroform extracts of tar produce by distilling tobacco at a temperature of 400-500 C. was applied to 50 mice for about 8 months, and again nothing but ulceration resulted; and, when the painting was suspended, the ulcers healed promptly. No warts were produced. The strain of albino mice used was the low spontaneous-cancer incidence. As a control, typical infiltrating squamous-cell epithelioma was produced with an extract of soot.

Bogen and Loomis (3227) also concluded from their experiments that tobacco-tar did not possess the irritating and epithelial-stimulating properties which lead to the production of neoplastic growths when tested on the skin of mice. Tar obtained by the destructive distillation of Kentucky Burley tobacco in a current carbon dioxide, and then purified by repeated extractions with sulfuric acid, alcohol, and ether, was diluted with equal parts of glycerine, and applied to an area 1 cm. in diameter on the back of the neck of 12 mice twice a week; in this strain of animals, spontaneous tumors had developed in less than 1% during the preceding 2 years. In addition, 12 mice of similar age, sex, and size were similarly treated with gas-house tar of known carcinogenic properties. The mice treated with tobacco-tar showed no marked changes in the skin and no carcinomatous changes, while the coal-tar-treated mice showed marked changes in the skin in a few days, and within a few months, papillomas appeared in almost every case, and eventually metastases appeared.

Hirst 1932, collected tar from tobacco mechanically smoked at 400-500 C. and at 700-800 C., and applied them in concentrations of 10-50% in alcohol, benzene, or glycerol to the skin of the back of the neck of mice at intervals of about 3 days for periods up to 22 months. A tumor developed in only 1 of 50 animals used; and, in comparison with the very high incidence of cancer in mice treated with coal-tar, this indicated to the author that tobacco was relatively unimportant in the causation of cancer.

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According to Schurch and Winterstein (3542); also Schurch 1936, tobacco (cigar) tar and its several fractions did not produce cancer in mice, either alone or in combination with mechanical and thermal irritation. Only loss of hair and some skin atrophy at the site of application was noted in 100 animals treated with whole tar containing nicotine once or twice weekly for 258 days, although many animals became ill and died of nicotine poisoning. Similar results were obtained using a thicker preparation of tar over a period of 265 days, and also using a nicotine-free tar headed to 130 C., or when the skin area was rubbed with emery paper previous to the application of tar. No cancers resulted from treatment of mice with various tar fractions having different distilling ranges. No polycyclic aromatic hydrocarbons were found in tar obtained from cigar-smoke, and the cancerogenic hydrocarbons carbons of coal-tar were not present in tobacco tar (3542).

J. A. Campbell (3742) reported painting 24 mice with concentrated tobacco-tar obtained from cigarettes mechanically smoked, twice weekly, and at the time of writing had obtained cancer of the skin in only 1 of these. From a later report, (Campbell (3953)), it appeared that the animals were treated for 20 months, and a typical epithelioma had developed in 1 animal and a typical pre-cancerous hyperplasis in another. Compared to road-tar, the author noted, this tobacco-tar was certainly not very active, but it apparently may give rise to cancer of the skin after prolonged application.

Taki (3737; see also Kinosita, 3711 for details) applied the ether-soluble nicotine-free fraction of tar from tobacco pipes twice weekly to the skin of 104 mice. Of these, 94 died in 110 days or less, and of the surviving 10 which had passed the 130-day mark, 2 showed squamous-cell epitheliomas and 3 showed papillomas; the first papilloma was noted after 85 days. Parts of one specimen of epithelioma showed sarcomatous appearance microscopically, such as is rarely seen in coal-tar cancers; the transplantation of this specimen was successfully accomplished through two generations." (pp 413, 414, ref. 6101)

Similarities and differences between cigarette tar and coal tar, revealed by animal experiments. Although Roffo repeatedly described the similarities between coal tar and tobacco tar, other contemporary investigators from Europe and North America disagreed. Schürch and Winterstein from the University Hospital of Zurich, found that distilled fractions of tobacco tar did not contain the polycyclic aromatic hydrocarbons present in coal tar (3542). Unlike Roffo, the Swiss investigators did not observe any carcinogenic

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effect on mouse and rabbit skin. Rabbits previously fed with cholesterol-rich food and skin painted with coal tar showed 'tar warts' from topical application of tobacco tar, instead of a malignant invading papilloma.

Cooper, Lamb, Sanders and Hirst from the University of Birmingham, England, conducted their investigation of tobacco tar on mice "specifically in reference to pipe smoking." They reasoned that since there was a well established occurrence of a "carcinogenic constituent in gas works tar", the possibility existed that tar formed during tobacco-smoking is causally associated with cancer of the lip, tongue, or throat (3230). Tobacco tar was produced by igniting leaf at 400-500°C. and 700-800°C. Among over fifty mice painted with tobacco tar and observed for up to 22 months, only one mouse developed epithelioma. They concluded that since only one tumor appeared compared with "the very high incidence of cancer in mice treated with coal tar, tobacco is relatively unimportant in the causation of cancer." The fluoresence spectrum of tobacco tar was diffuse (4400 to 4600 Au) unlike carcinogenic substances from coal tar that have distinct bands (4000, 4180, 4400 Au).

Experimental carcinogenesis in rats. During the 1930's, the rat was not used for skin painting. Instead, the rat was used to test carcinogenicity of tobacco extracts injected into tongue, gastrocnemius muscle or lung tissue, implanted as a pellet in the urinary bladder, or administered orally. The description by Larsen, Haag & Silvette was as follows:

> "Morpurgo (3557) made repeated injections of small amounts of an extract from the tips of strong-smoked cigars [details of preparation not stated] into the tongue and gastrocnemius muscles of a strain of white rats in which spontaneous tumors of the muscular tissue had never been observed. In 9 or 10 of such experiments, injection into the tongue was followed by a severe, extensive, and

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prolonged inflammation, with necrosis and active regeneration of transversely-striated fibers, the process developing into a severe atropy and lipomatosis of the muscles and the formation of a granuloma rich in giant cells and cysts; in 1 rat, dying after the third injection, a very atypical myoblastoma had formed in the region of the strongly inflamed tip of the tongue. No indication of blastomatous neoformation was ever found in the gastrocnemius muscle.

In 50 white rats fed tar (0.15ml. per 120 gm. body weight) from black commercial tobacco in their ordinary diet, lesions in the stomach were observed in 50% of the animals 5-30 months after starting treatment (Roffo 4112, 4211, 4212, 4214). The lesions began with a simple hemorrhagic ulcer, which later became necrotic, and finally developed into a round ulcer, which became cancerized as the last stage of the process. The cancers produced had the histological structure of adenocarcinoma. The gastric region which suffered most was the glandular zone.

Roffo (3126) placed in the bladder of 10 rats globules of resin in which tobacco-extract had been incorporated, and, in equal numbers of control animals, resin, the distillation product of tar, tricresol, or aniline oil. At the end of 8 months, papillary formations were found in the bladder in all cases. The lesions caused by tobacco were said to be of distinctly neoplastic type. Similar globules placed in the peritoneum and in the subcutaneous tissue of other rats became encysted, and globules placed in the stomach were eliminated. This same author recorded thedevelopment of a pulmonary carcinoma produced locally in a rat at the focus of the injection [apparently repeated] of 1 drop of tobacco-tar mixed with an equal part of bird-lime (Roffo, 4313). At death of the animal in 8 months, a tumor the size of a lentil was found in the upper lobe, and similar but smaller formations were distributed throughout the rest of the lung; histologically, the process presented the structure of a pavement carcinoma with horny globules.

Roffo (4211) claimed to have demonstrated the presence in, and to have isolated 1,2-benzprene from tobacco-tar, and the carcinogenic properties of this tobacco benzpyrene were said to have been demonstrated in rats." (pages 420-421, ref. 6101)

There were no control animals injected with substrate excluding tobacco. The question as to whether Roffo detected 1,2 Benzpyrene (Larsen's et al interpretation) or 3,4 benzpyrene, cannot be answered now because of differences in terminology used by Americans and British chemists during the 1930's. The question is raised again in Chapter IV.

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McNally, from Rush Medical College, failed to find tumor in the mouth or the back of rats following topical administration of tobacco tar. Although he did not analyze the tar, he recalled the literature relating to pyridine present both in tobacco tar and in English charcoal briquets (3224).

Bogen and Loomis from Olive View, California, followed his 1929 report on composition of cigarette smoke (2928) with the study of tar application on mice skin (3227). He noted that the cutaneous application of tar derived from destructive distillation of tobacco did not possess the irrtating and epithelial stimulating properties that led to the production of neoplastic growth. Mice treated with gas-house tar developed metastasizing epithelioma.

McCormick, from Toronto, in reviewing some medical aspects of tobacco, commented on alleged carcinogenicity of tobacco:

> " Relative to the effect of tobacco on the digestive and respiratory systems, recent work on the cancerogenic properties of certain hydrocarbon distillates seems of interest. It has long been known that workers who handle pitch, and others who are employed in the manufacture of briquets from pitch and coal dust, frequently suffer from skin cancer. Likewise, shale oil workers coming in contact with crude paraffin, a natural distillation product, and chimney sweeps exposed to soot, a distillation product of coal, are known to be unduly prone to skin cancer. Recently Cook, Hieger, Kennaway and Mayneord (3333), working in England, and Morton, Branch and Clapp, in America, were able to isolate from coal tar certain benzene derivatives, such as benzpyrene, dibenzanthracene and triphenylbenzene, which, when applied to the skin or injected subcutaneously in mice, would produce cancer. This discovery throws new light on the possible role of tobacco in the causation of cancer of the lip, mouth, stomach and lungs, affections notably predominant in males, who in smoking expose these parts to the irritant action of the distillation products of tobacco. Thus it seems that certain products of combustion and distillation of the organic matter of tobacco, aside from the thermal and mechanical irritation associated with smoking, may sensitize the skin and mucous membrane of the respiratory and upper digestive tracts to cancer." (pages 68-69 of ref. 3849)

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The topic of tobacco experimental carcinogenesis ends with a reminder to the reader that the original purpose of skin painting experiments was to identify carcinogenic substances in coal tar causing skin cancer in workers exposed to fossil fuel products. The application of tobacco tar experiments to mouth cancer and lung cancer were not accepted by most clinicians, with the exception of the few enumerated above and highlighted in Harris' SOA report.

There was no reported testing of cigarette smoke by inhalation in rats. In later decades, the rat lung became preferred experimental model for long term testing of suspected carcinogens and also to examine biochemical, functional and microscopic changes in carcinogenesis. After decades of testing in rats, there has been no positive results from long term cigarette smoke inhalation in rats.

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D. OCCUPATIONAL/ENVIRONMENTAL FACTORS

During the 1960's, it became apparent to government toxicologists and their consultants that occupational and environmental health hazards can be derived from the same human and animal studies. I have therefore adapted the terminology of occupational/environmental factors, although information was derived from workers or general population. Harris described etiologic factors other than tobacco smoking and are covered by the following blanket statements:

> "4.3. During the 1920s and 1930s, experimental scientists increasingly recognized that specific chemicals or mixtures of chemicals could cause cancer. Moreover, the scientific community increasingly acknowledged the complementary roles played by experimental studies in animals and clinical observations in humans. For example, epidemiological studies of bladder cancer among aniline dye workers ultimately lead to the experimental induction of bladder cancers by the chemical beta-naphthylamine in 1938.
>
> 4.4. Similarly, Passey's (1922) experimental finding of the carcinogenicity of soot extracts confirmed the frequent clinical observation of cancer in soot-exposed workers. Likewise, clinical observations of skin cancers in coal tar and pitch workers stimulated a detailed study of high-boiling fractions of coal tar distillates (e.g., Kennaway 1925). By the early 1930s, such studies had lead to the identification of at least two specific chemical carcinogens, dibenzanthracene and benzo(a)pyrene. (See references cited in Berenblum and Schoental 1947; U.S. Public Health Service 1964.)

Should counsel decide to present another expert witness, the above statements can be criticized briefly as follows: The 1938 episode relating to bladder cancer involved Hueper, the posthumous expert I have selected (see page 7). The clinical and laboratory studies on coal tar during the 1930's far exceeded those for cigarette smoking.

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Urinary Bladder Cancer.

The lack of a reference for Harris' SOA statement 4.3 was probably an attempt to minimize the contributions of Hueper in the field of occupational/ environmental cancer, and to wrongly characterize him as one who participated in a "critical counterattack" of the evidence that smoking caused lung cancer [SOA 6.15]. Hueper was accredited to have conducted the key experiment that proved administration of beta-naphthylamine caused bladder tumors in dogs (3850, 3851). He reviewed the complex literature (3450) prior to the experimental study and retrospectively reviewed how positive results in animals answered etiologic questions in human bladder cancer (3852). Hueper was respected by other researchers in aniline bladder cancer (3761) that included Henry, Kennaway & Kennaway (3128) who were also interested in coal tar cancer. It was rumored that Hueper left DuPont (3735) because of disagreements on publishing the results of key dog experiments.

Hueper wrote on other topics relating to chemical carcinogenesis such as: growth factor (3311, 3449), immunologic aspects (3231, 3448, 3639), tuberculosis (3045), neoarsphenamine (3332), polyvinvyl alcohol (3950), and ethylene glycol (3640, 3853). Some publications relating to host susceptibility to cancer are discussed under Topic E while industrial chemicals are discussed under Part Four as they relate to tobacco smoke constituents. Hueper did not publish articles on environmental factors, tobacco smoke and lung cancer during the 1930's although his earlier articles (2633, 2933) were cited by contemporary authors (3761).

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Lung Cancer Monographers.

As a general rule, monographers accepted the role of occupational/environmental factors in pulmonary carcinogenesis, more than that of tobacco smoke. Although all monographers favored the occupational/environmental etiology, some of them did not mention tobacco smoking.

Ewing: Neoplastic Diseases. This was a treatise on pathology and clinical aspects of all forms of tumors. The etiology section in the chapter entitled "Tumors of the Lung" included:

> "In mice that had inhaled road-dust containing from 2 to 3 per cent. of tar, Campbell observed a tenfold increase of adenoma of the lungs. Dust freed from tar gave much less increase, while cigarette-smoke and motor-gas gave a slight increase. Tobacco-smoke is especially incriminated by Roffo, who found spectroscopic evidence of phenanthrene in tobacco extracts, which produced a high proportion of papillomas of the skin. Lehmann found that smoking a 5-gm. cigar yields 200 mg. of inhaled tar, while an 8-hour drive 32 feet behind an automobile over a tarred road yields only 1.5 mg. of inhaled tar. The proportion of smokers among patients with lung cancer is very high (Roffo).
>
> Kennaway found no occupations to which the recorded increase of lung cancer could be attributed. Rural workers are as much affected as urban. Cotton-spinners who inhale air sprayed with an oil which produces cancer of the skin show a small incidence of lung cancer. Craver noted occupations causing exposure to various irritating dusts in 23 per cent. of his cases, and a history of marked previous respiratory infection in only 12 per cent." (page 873 of ref. 4001)

Ewing's bibliography had no listing for Lehmann and Roffo, indicating that the sentences must have been added to page proofs and could not be inserted into the run-on style of references. The paragraph on Kennaway did not reflect the fact that Campbell (preceding paragraph) favored occupational cause of lung cancer. Details of conflicting observations are discussed below. It suffices to reiterate that Ewing had not conducted research on lung cancer and favored theories in earlier editions which he subsequently retracted. Ewing passed

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away three years later and there was no subsequent opportunity to correct or revise the above statements.

Monographer (k) Fried: Primary Carcinoma of the Lung. The etiology section in this monograph (3201) also appeared in a review article (3101). The discussion was entitled "Inhalation of Tar Products:"

> "The role of chemical substances in the causation of epithelial malignant tumors was noted by clinicians before the advent of the experimental era of cancer formation. Older observers attributed epithelioma of the lip of pipe-smokers not only to the mechanical action of the pipe but to the tobacco as well. Similarly arsenic, anilin, paraffin, and many other substances were regarded as being carcinogenic by virtue of their chemical composition.
>
> The carcinogenic action of tar was for the first time demonstrated by Ichikawa and Yamagiwa (1513). These authorities have shown that when the rabbit's ear, which is never the seat of a spontan- eous tumor, is painted for a certain period of time with this chemical it develops a malignant tumor. These experiments have since been broadened and successfully applied in the causation of cancers of other structures in different animals, of which the mouse is the animal of choice. The customary technique consists in the application (painting) of tar to certain cutaneous areas, the applications being spaced at short intervals. The intimate mechanism of the neoplastic formation is not understood. With the microscope one notices damage to the skin caused by the chemical followed by excessive regeneration ending in malignant disease.
>
> An outstanding example of pulmonary neoplasms caused by chemical substances is frequently referred to in studies of the so-called "Schneeberger Pulmonary Cancer." The disease is reported to have occurred in a high percentage of workers in cobalt mines in the province of Saxony, Germany. While some investigators attributed the pulmonary new growth to inhalation of arsenic and cobalt, another group was inclined to regard the cancer as being due to chronic inflammatory changes in the lungs caused by the inhalation of dust, and so on. In fact, the incidence of the pulmonary cancers in the Schneeberger inhabitants has recently decreased, apparently as a result of improved hygienic conditions of the mines.
>
> An etiologic relationship between tar and primary bronchiogenic cancer in man was suggested by the reports of Möller (2423), and of Murphy and Sturm (2520). Möller, from Fibiger's laboratory, by painting the back of young rats with tar failed to obtain a cancer of the skin but found that all the experimental animals developed bronchiogenic cancer. Murphy and Sturm have obtained similar results with mice. They, too, have observed that

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the external application of tar to a number of separate areas on the surface of mice, in such fashion that no single area is irritated sufficiently long to cause lesions of the skin, has resulted in a very high incidence of typical epithelial pulmonary neoplasms, identical histologically to those found spontaneously in mice. Their previous experiments with transplantation of cancer had shown that repeated application of tar greatly reduces the animals resistance to cell growth. They believe, therefore, that the tar acted apparently only as a factor in lowering the resistance of the mice, while the pulmonary cancer was due to irritation by inhaled dust or particulate matter. (The mice lived in burrows under sawdust and shavings mixed with choped hay.)

Following the reports of these observers a few clinicians have, nevertheless, connected the claimed increase in pulmonary cancers with the modern application of tar to roads. Stäehelin (2526), Heilman (2528) and others suggested that tar, gasoline, and other substances used by automobile cars act in all probability as chemical irritants upon the bronchial tree, leading to epithelial malignant disease. Kimura (2321) claims to have produced pulmonary cancer by injecting tar into the trachea of laboratory animals. His experiments should be accepted with reservation, however, since only one rabbit and one guinea pig were used.

Smith (2826) by exposing mice to coal tar fumes, to fumes from the exhaust of an automobile, and also by painting the rodents with gasoline for a period of five months, could not produce carcinoma of the lungs in the coal tar series; it occurred once in 26 mice exposed to exhaust, and once in 29 mice painted with gasoline. This proportion, according to Smith, is not greater than the laboratory spontaneous occurrence of primary pulmonary cancers ordinarily found in white mice.

It is not at all certain that the alleged increase in the incidence of pulmonary cancers coincided with the inauguration of the custom of painting the roads with tar. Moreover, in Russia, where the primitively-built roads are not painted by tar, and where the number of automobile vehicles is infinitesimal, Davidoff, Uspensky and others have noted a marked increase in bronchiogenic cancers in the last ten years. It would appear, then, that the supposed recent increase in bronchiogenic cancers cannot be regarded as being the result of painting of roads with tar or its products." (pages 22-25 of ref. 3201)

The most important paragraph related to the evolution of concept that lung cancer appeared in mice skin-painted with coal tar. Fried favored the earlier available explanation that coal tar reduced animal resistance to cell growth. Before the decade was over, Andervont described for the first time that a pure

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chemical substance, applied to the skin or administered orally or by injection causes lung tumor, and that the susceptibility was influenced by cross-breeding. It is important to start recalling this series of experiments that were widely known in the 1930's, 1940's, and 1950's, but were overlooked in the 1960's to the present.

Monographer (d) Hruby & Sweany: Primary Carcinoma of the Lung, with special reference to incidence, early diagnosis and treatment. There was no mention of tobacco smoke in etiology. The occupational history of patients revealed the following:

> "As to the occupation, there seem to be few instances in which there is any relation to cancer of the lung. Claims have been made that automobile gas, smoke, irritating dusts and tar on roads are contributing causes, but in an analysis of a large number of case histories we were unable to find a tendency in favor of any occupation, trade, profession or station of life. Laborers, office workers, and housewives are most affected, but they are likewise the most numerous. Mechanics, automobile workers, painters, stokers and carpenters are involved about in proportion to their numbers. Perhaps the only instances in which the occupation may be suspected are the cases occurring in certain European mines. Incidence of cancer of the lung was shown by Arnstein to be high in the workers in the Schneeberg mines, but not in the surrounding population. Schmorl and others studied the problem and reported that arsenic is present in high proportions in the dust of these mines. The dust is also said to be radioactive. Pinchan and Sikl showed this in a study of the pitchblende mines of Joachimstal, Bohemia, across the mountains from Schneeberg. These are medical curiosities, however, and produce no great public health problem. Other minerals, such as nickel, cobalt and bismuth have also been accused, but they do not seem to cause any effect when mined elsewhere in the world." (page 507 of ref. 3302)

The role of radioactive gas and dust may have been "medical curiosities", but during the 1980's, there have been some concern on radon in houses in the northeast section of the United States.

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Monographer (g) Klotz: Primary Carcinoma of the Lung. In addition to the paragraph on tobacco smoking (see above Topic B), the paragraphs on environmental factors were as follows:

"The development of tarred roads led to much speculation as to a possible etiologic relationship. Some weight is lent to this idea by such observations as those of Kennaway and Kennaway (3632), who noted an increased incidence of cancer of the lung among open air workers exposed to road dusts. It seems remarkable, however, that this observation did not apply to motor vehicle operators who surely suffer a similar exposure. Though a high incidence of lung tumors has been reported from regions where road tarring is not practised, Campbell (3742) does not consider this an argument against an etiologic relationship, stating that dust from such roads may be carried tremendous distances by the air currents. This cannot, however, be considered tenable in view of reports from communities where the injurious agents would have to be carried hundreds or even thousands of miles. Campbell found a high incidence of warts which underwent malignant changes in laboratory animals exposed to dust from tarred roads, but no pulmonary neoplasms developed. Passey and Holmes, carefully analyzing the problem, point out that the alleged increase in lung cancer in Great Britain appeared prior to the tarring of roads. They further suggest that if the time factor required to produce growths in animals, as demonstrated by Campbell, were applied to man, the effect of road tarring should just now be making itself felt.

Fumes from gasoline engines and pollution of the air in industrial centers can be considered under the same category of etiologic agents as dusts from tarred roads. There is certainly no direct evidence to connect lung cancers with the first of these. Though a high incidence of carcinoma of the lung has been noted in some industrial centers where air pollution was great, an equally high incidence has been observed in rural communities. It has also been noted that there is no undue occurrence of the disease among mechanics and garage workers who are constantly exposed to a polluted atmosphere. Although Kimura (2321), reported an adenoma of the lung in a rabbit and an adenocarcinoma of the lung in a guinea-pig following the insufflation of coal tar, Smith (2826), was unable to produce pulmonary tumors in mice by exposing the animals to pitch fumes, products of an internal combustion engine, or by painting the skin with gasoline. Although Smith thus found nothing to support the theory that fumes from coal tar or gasoline were of importance in human cases of bronchial cancer, reports such as that of Kawahata are most suggestive. This investigator observed 12 cases of the disease among employees tending furnaces for gas production, where the air contained several tar derivatives with unknown carcinogenic properties. Recently, Seelig and Benignus (3648) found 8 adenocarcinomata of the lung in

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> 100 mice exposed to coal soot, while only 1 tumor developed in their controls. It must be concluded, however, that the evidence incriminating inhaled tar products as a cause of cancer of the lung in human beings is as yet far from convincing." (page 450-451 of ref. 3802)

The conflicting opinions between Campbell and Kennaways relate to workers and environmental pollution in Great Britain. There were differences in ambient air contamination levels but I have not yet found the necessary publications to document my recollection. For pulmonary emphysema, there was a difference in incidence and severity of British and American patients during the 1930's and 1940's.

Monographer (c) Simons: Primary Carcinoma of the Lung. Compared to other moographers, Simons wrote a more detailed review comparing tobacco smoke, street dust particles, motor exhaust fumes, and coal tar partcles. The etiologic reviews relating to each group of inhalants are reproduced completely below to recapture the human and animal studies as interpreted by one monographer, Simons, who, unlike Ewing, conducted original studies on lung cancer.

> "Dust Inhalation. Hampeln (2328) proposed that pulmonary carcinoma is a dust inhalation disease and explained the increased number of these neoplasms as due to the increase of dust produced by the growth of traffic and industry. It was he who directed attention to the fact that in large cities, such as Oslo, where sanitary and hygienic measures were not interrupted by the War but instead were improved by modern technical knowledge, no increase of frequency of pulmonary malignancies has been noted. The difference between Oslo and Riga, where dust constitutes a real menace and where a marked increase in primary cancer of the lung has taken place, he considered proof of his contention that dust is the main etiologic factor.
>
> Not only dust but smoke and chemical impurities in the air have increased along with the growth and concentration of industry, said Heilmann (2528). He showed that the pathologic changes induced by dust in the lungs present a histologic picture, the ultimate sequence of which is carcinomatous. Materna too, considered street dust the prime etiologic factor in pulmonary carcinoma because both have increased during recent years.

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Supporting this view, Folgers found pulmonary cancers more frequently in horses, dogs and other animals exposed to street dust than among cattle and others unexposed. Seyfarth (2421) found that men whose vocations expose them to the inhalation of fine solid particles are more often affected than others; this is the reason, he believed, that the right lung is involved most often. Schmorl (2329) insisted that the increase of lung cancers in Dresden is traceable to the sandstone industry and coal mines. Seyfarth denied that any one kind of dust - street dust, stone dust, metal dust, glass or coal dust - can be held solely responsible.

Duguid (2721) reasoned that the single fact that tumors arise in tissues directly exposed to the atmosphere encourages the suspicion that atmospheric impurities may be an important cause of intrathoracic new growths. It must be, he continued, some specific type of pollution rather than general pollution; for the smoke abatement act has cleared English cities of smoke, and hence if intrathoracic tumors were due simply to smoky atmospehere they would have decreased since the passage of that act, which is not true. But they may be due to dampness of the atmosphere causing bronchial catarrah, which may be sufficiently irritating to cause cancer. Assmann (2422) called attention to the frequency of lung cancers in two large cities of Saxony. Especially notable are the high percentages of the Seyfarth (2421) statistics for Leipzig as compared with which Assmann gave the low values of this statistics for Dortmund and referred to the rarity of pulmonary cancer in the Ruhr region and Upper Silesia. He then suggested that it is not so much coal dust in general as dust of the brown coal in Leipzig which should be considered. More recently, the Kennaways (3632), in analyzing 18,280 death certificates of males who had died in England or Wales between 1920 and 1933 as a result of carcinoma of the lungs or larynx, found that a group of open air occupations in which there is prolonged and excessive exposure to the dust of roads has a high incidence of these two forms of cancer.

To the contrary, Berblinger (3134), after examining 12 cases on this point specifically and finding no evidence of chalicosis or anthroacosis in any of the specimens, denied that dust of itself is a cause of lung cancers in any locality. Kikuth (2527) preferred to leave open the question of increased dust in the larger cities, because, regardless of its quantity, it has changed in quality, at least in respect to a relatively higher mixture of benzene fumes. He believed that street dust plays no great part in the etiology of pulmonary cancer, pointing out that there has been an appreciable increase of lung tumors in Jena, a small city with little increase of traffic. Rare discoveries of secondary pneumonoconiosis in pulmonary carcinomas, as reported by Siegmund and Helly, did not impel Probst (2732) to assign a leading role to street dust as a cause of lung cancers. His material demonstrates that teamsters, street workers, policemen, chauffeurs and other

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workers especially exposed to street dust show no high incidence of lung tumors.

Thus far, then, street dust has not been demonstrated to be of great importance in causing pulmonary carcinomas. But it may be conceded to be a contributing factor and, in some instances, even the primary etiologic agent. If it is emphasized as a cause, that can be only through its character as a chronic mechanical or chemical lung irritant." ((pages 77-79 of ref. 3702)

Simons, as a thorough and meticulous monographer, reconciled conflicting observations by grouping dust inhalation studies, regardless of whether there were any chemical irritants. In the above discussion, the remarks refer both to occupational exposure of miners as well as to non-occupational or ambient air exposure of general population. The next discussion on motor exhaust fumes refer both for workers, i.e., chauffers, bus drivers, garage operators, tunnel guards, and the general population exposed to motor vehicular exhaust.

"Motor exhaust fumes. Duguid (2721) mentioned the exhaust gases of motor drawn vehicles as possible causes of pulmonary cancers, and Klotz said: 'It is true that the incidence of carcinomas of the lung shows a parallelism with the increased use of automobiles' (2722). According to Heilmann (2528), the exhaust of internal combustion motors and smoke with its by-products are related to tar, whence one may ascribe to them an influence of bronchial mucous membranes already damaged by chronic irritation. But Bloch and Widmer proved that active fractions of coal tar under 230 degrees and 1-2 mm. mercury pressure (the equivalent of 480 degrees normal pressure) contain no, or in all events few, carcinogenic ingredients.

The substance of Probst's (2732) exhaustive treatment of this topic is as follows: The question is whether or not auto exhaust gases contain substances similar to the coal tar derivatives. Data supplied by Professor Schlapfer, director of the laboratory for combustible material at the Union Technical High School, Zurich, show that tars obtained from petroleum products during the process of combustion have an aromatic character only when the disintegrating temperatures reach 900 degrees or more, which seldom occurs in the cylinger walls of gas motors. He reasoned, then, that aromatic combinations with high boiling points such as are found in coal tars do not originate in the internal combustion motors, while it follows that their exhaust gases contain no combinations related to the coal tar products or derivatives with which cancer was produced experimentally in animals. Probst proceeded to state that the traffic of Zurich refutes the views of

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> Heilmann, citing the table placed at his disposal by the Bureau of Motor Control of the canton of Zurich. Comparison of these figures with those on the frequency of incidence of pulmonary carcinoma in that locality bears out his position. Further, he recalled that motor traffic was greatly curtailed during the War by shortgage of fuel and that it was during this period that an increase of the disease occurred. Finally, in the vocational data on his cases, no patients were found to be especially exposed to motor exhausts, as are automobile mechanics or chauffeurs.
>
> The case against the motor car, said Passey and Holmes (3537), is supported by two schools, one of which blames exhaust fumes while the other holds tarred roads responsible. But neither garage workers on one hand, nor professional drivers on the other, are especially prone to develop pulmonary neoplasms. In 1936, Schmidtmann, of Stuttgart, reported that the waste gases from gasoline motors have no effect on the bronchial mucosa even after many years of exposure, whereas gases from oil-driven motors cause marked dust deposits with callus formation of the lungs, destruction of the bronchioles, emphysema and symptoms of atelectasis. No infiltrating epithelial growth has yet been observed.
>
> While the belief that there is a causal relationship between motor exhaust gases and pulmonary cancer is alluring, it lacks sound proof." (pages 82-83 of ref. 3702)

Since most of the discussion reviewed vehicular traffic in European cities, I have not obtained all foreign references but selected a few, identified by a four-digit bibliography number.

In the United States, prior to the passage of the Clean Air Act of 1970, there was considerable literature that has convinced me that Simon's statement can be revised as follows: Causal relationship between motor exhaust gases and pulmonary cancer was not only alluring during the 1930's, but was also supported by several human and animal exposure studies prior to 1970.

> "Inhalation of tar particles. In discussing tar particles in etiology, Katz (2731) said: 'How far tar, in the form of auto exhaust gases and street tarring, plays a role cannot be decided at present, since it has been established that tar represents an aspecific or only a relatively specific irritant. Automobile traffic has increased enormously during recent years, but whether the tar derivatives or street dust are to be blamed in our problem cannot be said. City dwellers do not predominate in my series of

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